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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Akira NAKAGAWARA et al.

Application No.: 10/570,346

Filed: March 3, 2006 Attorney Docket No.: 7388/88083

Confirmation No.: 1857 Customer No.: 42798

SUBMISSION OF INTERNATIONAL PRELIMIANRY EXAMINATION REPORT

Commissioner for Patents
Customer Service Window
Randolph Building
401 Dulany Street
Alexandria, VA 22314

Sir:

Applicants submit herewith a copy of the English translation of the International Preliminary Examination Report (IPER) issued for the basic PCT application (PCT/JP2004/012955) of the above-referenced application. Please make the IPER of record herein.

Respectfully submitted,

FITCH, EVEN, TABIN & FLANNERY

Date: **July 26, 2006**

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference FP04-0304-00	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/JP2004/012955	International filing date *(day/month/year)* 06 September 2004 (06.09.2004)	Priority date *(day/month/year)* 05 September 2003 (05.09.2003)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant HISAMITSU PHARMACEUTICAL CO., INC.		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☒	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 20 June 2006 (20.06.2006)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Masashi Honda
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PATENT COOPERATION TREATY

TRANSLATION

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

	Date of mailing *(day/month/year)*
Applicant's or agent's file reference FP04-0304-00	FOR FURTHER ACTION See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/JP2004/012955	06.09.2004	05.09.2003

International Patent Classification (IPC) or both national classification and IPC

Applicant
HISAMITSU PHARMACEUTICAL CO., INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I — Basis of the opinion
- ☒ Box No. II — Priority
- ☐ Box No. III — Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV — Lack of unity of invention
- ☒ Box No. V — Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI — Certain documents cited
- ☐ Box No. VII — Certain defects in the international application
- ☐ Box No. VIII — Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/JP	Authorized officer
Facsimile No.	Telephone No.

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/JP2004/012955

Box No. I Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This opinion has been established on the basis of a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of international search (under Rule 12.3 and 23.1(b)).

2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

☒ a sequence listing

☐ table(s) related to the sequence listing

b. format of material

☐ in written format

☒ in computer readable form

c. time of filing/furnishing

☐ contained in the international application as filed.

☒ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/JP2004/012955

Box No. II Priority

1. ☐ The following document has not yet been furnished:

   ☐ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date in the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

The previous application that forms the basis for the priority claim of this international application contains no description of the inventions of claims 4-9 and part of claim 10 of the present application. Therefore, in this written opinion the filing date of this international application is considered to be the relevant date for the inventions of those claims.

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/JP2004/012955

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1, 3-5, 7, 9, 10	YES
	Claims	2, 6, 8	NO
Inventive step (IS)	Claims	3	YES
	Claims	1, 2, 4-10	NO
Industrial applicability (IA)	Claims	1-10	YES
	Claims		NO

2. Citations and explanations:

Document 1: WO 02/79500 A1 (BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM) 10 October 2002

Document 2: PARK, C. H. et al., Involvement of p53, JNK and NK-κB in in CT-induced neuronal apoptosis. Society for Neuroscience Abstracts, 2001, Volume 27, Number 1, p. 1439. (abstract) BIOSIS [online]; BIOSIS Accession No. 2001:547435

Document 3: KINOSHITA, A. et al., The gamma secretase-generated carboxyl-terminal domain of the amyloid precursor protein induces apoptosis via Tip60 in H4 cells. J. Biol. Chem., 2002, Vol. 277, No. 32, p. 28530-6

Document 4: SIONOV, R. V. et al., The cellular response to p53: the decision between life and death., Oncogene, 1999, Vol. 18, No. 45, p. 6145-57

Document 5: ARAKI, Y. et al., Coordinated metabolism of Alcadein and amyloid beta-protein precursor regulates FE65-dependent gene transactivation. J. Biol. Chem., 2004 Jun, Vol. 279, No. 23, p. 24343-54

Document 1 cited in the international search report states that the C-terminus of APP forms a complex with Fe65 and Tip60; that this complex activates transcription; and that it is important to identify substances that affect the cleavage of APP because such compounds are important drug candidates for the treatment of Alzheimer's disease (page 5, lines 2 to 13). In addition, document 1 states that binding between the two substances occurs via the NPTY sequence of the C-terminus of APP and the PTB2 domain of Fe65 (page 32, lines 2 to 7; page 35, lines 26 to 28).

Document 2 states that the C-terminal fragment (CT) of APP is suspected of being a candidate for the pathogenesis of Alzheimer's disease, and that CT is thought to promote the expression of p53 and cause neuronal apoptosis.

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of: Box V.

Document 3 states that the C-terminal fragment of APP (APP-CT) forms a complex with Tip60, that Tip60 is involved in apoptosis induced by APP-CT, and that the γ-cut of APP may be one cause of nerve degeneration associated with Alzheimer's disease (in particular, see abstract).

Document 4 states that c-Abl and $p19^{ARF}$ are protein substances that antagonistically inhibit the binding of Mdm2 to p53 (see page 6150).

Document 5 states that AlcICD is believed to competitively inhibit the binding of the intracellular domain fragment of APP with Fe65 (in particular, see abstract).

oClaims 2, 6, and 8

Document 1describes a method for identifying compounds that the kind of cleavage of APP that produces an APP C-terminal fragment (which this authority finds to be equivalent to AICD in the inventions of the present application) (see claim 1), and it states that such compounds are important candidates for the treatment of Alzheimer's disease (see page 5, lines 2 to 13).

Because this authority finds that compounds that inhibit the production of AICD from APP are included in compounds that inhibit the interactions between AICD and either p53, Fe65, or Tip60, the inventions of claims 2, 6, and 8 lack novelty and an inventive step with respect to document 1.

oClaims 7, 9, and 10

Documents 1-5 cited in the international search report do not describe the inventions of claims 7, 9, and 10, and therefore these inventions are novel.

Document 1 does not describe the screening of compounds that inhibit interaction between AICD either Fe65 or Tip60. However, judging from the mechanism described in document 1 (see Fig. 8), compounds that inhibit the interaction of AICD and either Fe65 or Tip60 can be assumed to be candidate substances for the treatment of Alzheimer's disease just as in the case of compounds that affect APP cleavage.

Therefore, this authority finds that persons skilled in the art can easily perform screening to distinguish compounds that inhibit the interaction of AICD and either Fe65 or Tip60 using conventional means.

Moreover, this authority finds that no particularly outstanding effect is provided thereby.

As a result, the inventions of claims 7, 9, and 10 lack an inventive step with respect to document 1.

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of: Box V.

oClaim 5

Documents 1-5 cited in the international search report do not describe the invention of claim 5 of the present application, and therefore this invention is novel.

Because document 1 states that binding between the two substances occurs via the NPTY sequence of the C-terminus of APP and the PTB2 domain of Fe65, it demonstrates that the interaction between AICD and Fe65 can be inhibited by using peptides containing these amino acid sequences.

As noted above, because compounds that inhibit the interaction between AICD and Fe65 can be assumed to be candidate substances for the treatment of Alzheimer's disease, this authority finds that persons skilled in the art can easily attempt to use the aforementioned peptides for the treatment of Alzheimer's disease.

In addition, there are no examples in the Description of the present application wherein the above peptides are actually used in the treatment of Alzheimer's disease, and this authority finds that no particularly outstanding effect is provided thereby.

As a result, the invention of claim 5 lacks an inventive step with respect to document 1.

oClaim 4

Documents 1-5 cited in the international search report do not describe the invention of claim 4 of the present application, and therefore this invention is novel.

Document 5 states that AlcICD is believed to inhibit the binding of APP with Fe65.

As noted above, because compounds that inhibit the interaction between AICD and Fe65 can be assumed to be candidate substances for the treatment of Alzheimer's disease, this authority finds that persons skilled in the art can easily attempt to use AlcICD for the treatment of Alzheimer's disease.

In addition, there are no examples in the Description of the present application wherein AlcICD is actually used in the treatment of Alzheimer's disease, and this authority finds that no particularly outstanding effect is provided thereby.

As a result, the invention of claim 4 lacks an inventive step with respect to documents 1 and 5.

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of: Box V.

oClaim 2

Document 2 states that the C-terminal fragment (CT) of APP (which this authority finds to be equivalent to AICD in the inventions of the present application) is thought to promote the expression of p53 and cause neuronal apoptosis. This description implies that if there is a drug that inhibits the aforementioned interaction between AICD and p53, it will be useful for the treatment of Alzheimer's disease.

As a result, this authority finds that persons skilled in the art can easily perform screening to distinguish compounds that inhibit the interaction of AICD and p53.

Moreover, no particularly outstanding effect is provided thereby.

As a result, the invention of claim 2 lacks an inventive step with respect to document 2.

oClaim 1

Documents 1-5 cited in the international search report do not describe the invention of claim 1 of the present application, and therefore this invention is novel.

From the description in document 4, the possibility is shown that that c-Abl and $p19^{ARF}$ are drugs that can inhibit the interaction between AICD and p53.

As noted above, this implies that if there is a drug that inhibits the aforementioned interaction between AICD and p53, it will be useful for the treatment of Alzheimer's disease. Therefore, this authority finds that persons skilled in the art can easily attempt to use c-Abl and $p19^{ARF}$ for the treatment of Alzheimer's disease.

In addition, there are no Examples in the Description of the present application wherein use c-Abl and $p19^{ARF}$ are actually used in the treatment of Alzheimer's disease, and this authority finds that no particularly outstanding effect is provided thereby.

As a result, the invention of claim 1 lacks an inventive step with respect to documents 2 and 4.

oClaim 3

Documents 1-5 cited in the international search report do not describe the invention of claim 3 of the present application, and therefore this invention is novel.

None of the documents states that AICD and p53 form a complex, and this authority finds that such a matter is not obvious to persons skilled in the art. Therefore, the invention of claim 3 of the present application involves an inventive step with respect to documents 1-5

It should be noted that in this written opinion the filing date of this international application is considered to be the relevant date for the inventions of claims 4-9 and part of claim 10.